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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,721	11/19/2001	Avi J. Ashkenazi	P2730P1C55	2434

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HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CO 94025-3506

EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,721	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *122-126,129-131 and 135-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *122-126,129-131 and 135-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/4/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 122-126, 129-131 and 135-138 are pending and under consideration.

The previous rejections under 35 U.S.C. §112, second paragraph are withdrawn in view of applicants amendments.

The rejection of claims 119-138 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention (deposit requirement) is withdrawn in view of applicants amendments.

The rejection of claims 119-123 and 132-138 are rejected over locus H74303, claims 119-121 and 132-138 are rejected over locus H58326, claims 119-121 and 132-138 are rejected over locus H73373, and claims 132-134 are rejected over locus RO2548 is withdrawn in view of the amendments to the claims.

Formal Matters

The new title of the invention is acknowledged.

Objections and Rejections under 35 U.S.C. §§ 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 122-126, 129-131 and 135-138 are rejected under §35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility. This rejection is maintained for reasons of record in the Office Action mailed 6/3/2004 at pages 3-4.

Applicants traversal of this rejection, filed 11/3/2004, has been fully considered but is not deemed persuasive. It is noted that applicants have amended the claims to recite that the

claimed nucleic acid is "amplified in lung tumors". . However, as set forth in the previous Office Action, it is not amplified consistently enough to support a diagnostic utility for the claimed nucleic acids. Further, the recitation of such raises issues under 35 U.S.C. §112, first paragraph regarding written description (see below), and fails to provide utility, because no significant association between the claimed nucleic acids and lung cancer, such as would lend diagnostic utility, has been disclosed or established, as set forth in the previous Office Action.

The Declaration by Dr. Goddard has been fully considered but is not deemed persuasive.

Dr. Goddard states at paragraph 7 that "It is my personal experience that the quantitative TaqMan PCR technique is technically sensitive enough to detect at least a 2-fold increase in gene copy number relative to control. It is further my considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e. a non-tumor) sample is significant and useful..." This has been fully considered but is not deemed persuasive, as the issue, as presented at page 4 of the previous Office action is *not* whether the technique is sensitive enough to detect a two-fold difference in amount of DNA, but rather that such was detected in only a minority of the tested lines of human lung tumor cell lines, which increase is likely to be due to aneuploidy in the tumorous tissue, and is neither diagnostic of cancer, nor evidence of overexpression, which is the actual presence of extra protein encoded *by* the nucleic acid. It remains that the sequence of PRO809 was found at no more than two copies per cell, and only in a minority of tumors tested. The person of ordinary skill in the art would not consider the results to be significant or diagnostic in view of the review by Sen. Declarant's statement of opinion regarding the significance of a two-fold increase has been considered but is not deemed persuasive, as it is not supported by fact or evidence, but rather is merely conclusory in nature, and is also not supported by the art. Sen has been previously discussed. Even if the nucleic acid were shown to be present in additional copy at the mRNA level, as opposed to merely being due to extra copies of the relevant chromosomes, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to

normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

At page 8, applicants argue that both the Examiner and Sen teach that aneuploid tissues are cancerous of pre-cancerous. This argument has been fully considered but is not deemed persuasive. Applicants statement is erroneous. Sen includes no teaching that all aneuploid tissues are cancerous or pre-cancerous, nor did the Examiner make any such statement. Rather, both Sen and the Examiner state that cancerous tissues are known to be aneuploid. It is also true that pre-cancerous tissues *may* be aneuploid. The converse is *not* true. Aneuploidy is also a feature of damaged tissue, and is commonly found in colon and lung tissues, which are subject to environmental damage. It does not invariably lead to cancer.

In the Ashkenazi Declaration filed under 37 CFR 1.132 (dated 9/15/2003 and filed 11/3/2004), Declarant argues that "detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes." This argument is not persuasive, as in the instant case it has not been established that the changes in the amount of DNA were significant. They occurred in only a minority of samples of the particular lung cancer types, and cannot be considered to be diagnostic in the absence of significance, that is a statistically significant correlation between increased copy number and cancer. It remains that random aneuploidy is the most parsimonious explanation of the results in the specification.

Declarant also argues that even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 122-126, 129-131 and 135-138 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 122-124, and 135-138 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record in the previous Office Action.

Applicants traversal that the recitation of a functional property in the claims overcomes the rejection. It is noted that the recitation "the nucleic acid encoding said polypeptide is amplified in lung tumors" is not a functional recitation *per se,* but rather a descriptor of where one might encounter the claimed nucleic acids. This argument has been fully considered but is not deemed persuasive because applicants have not established that there is any conception of nucleic acids in a manner commensurate in scope with the claims. All applicants have presented is a single nucleic acid found to be slightly amplified in a small proportion of cancers, and the germ of an idea that there might be variants of the nucleic acid that would be similarly associated. There is no evidence of the actual conception of such nucleic acids, nor is there any evidence of record that they exist. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and

Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. Accordingly, the rejection is maintained.

Rejections Over Prior Art

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 122-126, 129-131 and 135-138 remain rejected under 35 U.S.C. 102(b) as being anticipated by clone H74302, isolated by L. Hillier et al., WashUMerck EST Project 1995. By applicants admission at page 454 of the specification , the clone that was sequenced and designated DNA57836-1338 or PRO809, was purchased from Merck under clone designation H74302. According to NCBI, the cDNA was double stranded, and inserted in the "Lafmid BA vector", which was propagated in E. coli cells. With respect to claim 136, the DNA would necessarily have been "operably linked" to sequences in the vector for control of replication of the vector.

Applicants argument at page 10 of the response has been fully considered but is not deemed persuasive. The specification clearly states that the clone was purchased from Merck, and sequenced to obtain the sequence identified as PRO809. Applicants allegation to the contrary, in the absence of evidence, is not persuasive. In order to overcome this rejection, applicants must submit evidence in appropriate form as to what the actual sequence of the clone was, including an alignment to the claimed nucleic acids, in order for the Examiner to make a factual determination contrary to the admissions in the specification.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner

2/18/05